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Incorporation of the 8th Edition AJCC/TNM Staging of Carcinoma of the Appendix into the Esquivel Peritoneal Surface Disease Severity Score (E-PSDSS) in 229 Patients with Mucinous Appendiceal Neoplasms

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Abstract

Introduction: A practical staging classification that has prognostic significance in mucinous appendiceal neoplasms represents an unmet need in oncology. The purpose of this study is to present a second edition of the PSDSS in mucinous appendiceal neoplasms with or without peritoneal dissemination based on the AJCC/TNM 8th edition. **Materials and Methods:** We analyzed 229 patients based on the AJCC/TNM 8th edition incorporating G (grade) and E (extent of disease). The impact of these 5 clinicopathological variables (T, N, M, G, E) is scored as stages 0 to IV and is reported as the Esquivel Peritoneal Surface Disease Severity Score (E-PSDSS). **Results:** One hundred and seventy-three patients underwent cytoreductive surgery (CRS) and HIPEC. There were 30 (13.1%), 56 (24.4%), 48 (20.9%), 20 (8.7%) and 75 (32.7%) patients with E-PSDSS 0, I, II, III, and IV, respectively. Five-year overall survival was 100%, 100%, 84.46%, 52.29% and 12.92% for E-PSDSS 0, I, II, III and IV, respectively ($p < 0.0001$). On multivariate analysis, sex ($p = 0.0462$) and E-PSDSS stage [0, I, II, III, IV] (HR 0 vs IV NR, HR 1 vs IV NR, HR II vs IV 0.072 [95% CI 0.028, 0.189], HR III vs IV 0.353 [95% CI 0.158, 0.791]; $p < 0.0001$) were identified as independent predictors of survival. **Conclusion:** The E-PSDSS combines specimen examination and reporting according to the College of American Pathologists with the pTNM requirements from the AJCC staging manual. It represents an important prognostic indicator in patients with mucinous appendiceal neoplasms.

Keywords

Appendix Cancer, HIPEC, PSDSS

1. Introduction

Our understanding of mucinous appendiceal neoplasms has grown tremendously over the past two decades. The American Joint Committee on Cancer (AJCC) on their 7th edition, classified appendiceal carcinomas separately from colorectal carcinomas in 2010 for the first time [1]. In addition, it incorporated the histological grade into the TNM staging, classifying mucinous carcinomas into two distinct groups: low grade, composed of well differentiated carcinomas, and high grade, composed of moderately and poorly differentiated carcinomas [1]. A few years later, Asare *et al.*, published a manuscript demonstrating the strong prognostic impact and the distinctly different cancer specific survival between Stage IV patients with moderately versus poorly differentiated mucinous adenocarcinomas of the appendix [2].

The Peritoneal Surface Disease Severity Score (PSDSS) was introduced as a basis of stratifying patients with colorectal cancer with peritoneal dissemination [3]. Analysis of 5 publications on this subject demonstrates that the PSDSS on multivariate analysis was an independent predictive factor associated with survival [4].

In 2014, our group published an evaluation of the PSDSS in patients with mucinous appendiceal neoplasms, demonstrating also a very strong impact on survival based on the burden of disease as measured by the Peritoneal Cancer Index (PCI) [5]. This scoring system did not become widely accepted because common terminology, like the one used by all pathologists world-wide is mandatory for success.

In 2018, the 8th edition of the AJCC/TNM staging for carcinomas of the appendix, included G 1, 2 and 3 for well, moderately or poorly differentiated grades respectively [6]. This new edition constitutes significant progress as we now can classify patients based on a TNMG (Tumor, Nodes, Metastasis and Grade). However, under this latest staging, a patient with a LAMN (Low grade appendiceal mucinous neoplasm) with one minute mucinous deposit in the omentum and a patient with a signet ring cell carcinoma of the appendix with massive peritoneal dissemination are both Stage IV. Consequently, how to counsel a patient with a newly diagnosed appendiceal neoplasm remains an unmet need.

Due to the overall good prognosis of many of these patients, a prospective randomized clinical trial with a risk stratified cohort of patients would require substantial accrual and a very long follow up, making such a study not feasible.

Therefore, a decision-analysis modeling approach based on clinical and pathological variables commonly described by the healthcare providers seeing these patients is preferred. We have learned that the 3 most important compo-

nents of a scoring and/or staging system include: 1) Evaluation of a patient at the time of diagnosis, 2) Use of accepted/reproducible nomenclature and 3) Have prognostic significance.

The purpose of this study is to present a second edition of the PSDSS in mucinous appendiceal neoplasms with or without peritoneal dissemination based on the AJCC/TNM 8th edition staging but incorporating the G (grade) and E (extent of disease). The impact of these 5 clinicopathological variables (T, N, M, G, E) is scored as stages 0 to IV and is reported as the Esquivel Peritoneal Surface Disease Severity Score (E-PSDSS).

2. Materials and Methods

2.1. Selection of Patients

The clinical records of all patients in a prospectively collected peritoneal surface malignancy database from January 2005 to January 2013 had been previously reviewed and reported as the 1st edition of the PSDSS [5]. This study was conducted under the guidelines of our Institutional Review Board.

For this study, we staged those 229 patients based on the 8th edition of the AJCC/TNM following the protocol for the examination of specimens from patients with carcinoma of the appendix as recently published by the College of American Pathologists [7]. We then analysed their survival outcome based on this staging (**Figure 1**).

We then created the second edition of the PSDSS, the E-PSDSS, incorporating the TNM and histologic grade nomenclature as described on the 8th edition of the AJCC staging manual but also adding an E category to quantify the extent of

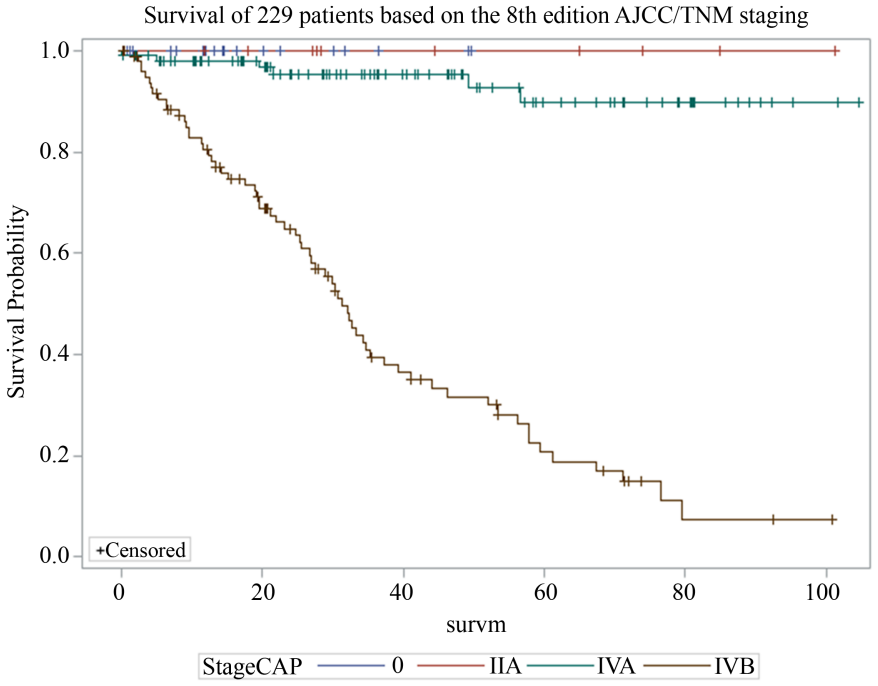

Figure 1. Survival of 229 patients based on the 8th edition AJCC/TNM staging.

peritoneal dissemination (TNMGE). Tumor burden was assessed by the Peritoneal Cancer Index (PCI); the PCI could be the one at the time of surgery or by CT scan in those patients without surgery and was reported as follows: E0, no peritoneal dissemination identified by imaging studies and/or during surgery; E1, low volume, PCI of 10 or less; E2, moderate volume, PCI more than 10 but less than 20; and E3, high volume, PCI greater than 20 (Table 1).

Overall survival was analyzed according to five tiers of estimated disease severity based on the above parameters and a comparison was made between patients that had CRS and HIPEC and those who did not as previously reported.

Table 1. E-PSDSS (Esquivel Peritoneal Surface Disease Severity Score).

E-PSDSS	T	N	M	G	E
0	Any	0	0	1	0
	T1 - 3	0	0	2, 3	0
I A	T4a, b	0	0	2, 3	0
I B	Any	0	1a, b	1	1 - 2
II A	Any	1	0	Any	0
	Any	Any	1a, b	2	1
II B	Any	2	0	Any	0
	Any	Any	1a, b	1	3
III A	Any	Any	1a, b	2	2
III B	Any	Any	1a, b	3	1
IV A	Any	Any	1a, b	2	3
IV B	Any	Any	1a, b	3	2 - 3
IV C	Any	Any	1c	Any	Any

Primary tumor (pT): Tx: primary tumor cannot be assessed; T0: No evidence of primary tumor; Tis: carcinoma in situ; Tis (LAMN): low grade appendiceal mucinous neoplasm confined by the muscularis propria; acellular mucin or mucinous epithelium may invade into the muscularis propria; T1: tumor invades the submucosa; T2: tumor invades the muscularis propria; T3: tumor invades through the muscularis propria into the subserosa or mesoappendix; T4: tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or the serosa of the mesoappendix or directly invades adjacent organs or structures; T4a: tumor invades through the visceral peritoneum; T4b: tumor directly invades or adheres to adjacent organs or structures. **Regional lymph nodes (pN):** Nx: regional lymph nodes cannot be assessed; N0: no regional lymph node metastasis; N1: one to three regional lymph nodes are positive; N2: four or more regional lymph nodes are positive. **Distant metastasis (M):** M0: no distant metastasis; M1: distant metastasis; M1a: intraperitoneal acellular mucin, without identifiable tumor cells; M1b: intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells; M1c: metastasis to sites other than the peritoneum. **Histologic Grade (pG):** Gx: grade cannot be assessed; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated. **Extent of disease by PCI (E):** E0: no evidence of peritoneal disease; E1: low PCI; 10 or less; E2: moderate PCI; 11 - 20; E3: extensive PCI; 21 or higher.

2.2. Statistical Analysis

The data collected were analyzed using SAS University Edition 2. Overall survival functions were compared among different groups using Kaplan-Meier estimators and log rank tests. A Cox proportional hazards regression model was applied to study the partial effect of each covariate after adjusting for the effects of other covariates in a multivariate analysis. Follow-up time was calculated from the date of surgery to the date of last follow-up for those having HIPEC and for those having no additional surgery; their follow-up time was calculated from time of diagnosis to the date of last follow-up. A p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patients Characteristics

As reported in the previous study [5], there were 135 (59%) females and 94 (41%) males among these patients. The median patient age was 52 years (range 21 - 79). About 75% of all 229 patients (173 patients) underwent CRS and HIPEC and their mean follow-up time was 34.6 months. There were 30 (13.1%), 56 (24.45%), 48 (20.96%), 20 (8.73%) and 75 (32.75%) patients with E-PSDSS 0, I, II, III, and IV, respectively.

3.2. Results of Patients Undergoing CRS and HIPEC by the E-PSDSS

One hundred and seventy three patients (75.5%) underwent CRS and HIPEC. There were 7 (4.05%) with E-PSDSS 0, 48 (27.75%) with E-PSDSS I, 46 (26.59%) patients with E-PSDSS II (8 in IIA, 38 in IIB), 19 (10.98%) patients with E-PSDSS III (10 in IIIA and 9 IIIB) and 53 (30.64%) patients with E-PSDSS IV (30 IVA and 23 IVB).

3.3. Results of Patients with No HIPEC by the E-PSDSS

There were 56 (24.45%) patients who did not have HIPEC. Twenty-three (41.07%) were staged as E-PSDSS 0. Eight patients (14.29%) were E-PSDSS I, 2 patients (3.57%) were E-PSDSS II, one patient (1.79%) E-PSDSS III and 22 patients (39.29%) were E-PSDSS IV.

3.4. Survival

Median overall survival of 166 patients in the CRS and HIPEC group with E-PSDSS I-IV was 76.6 months (95% CI 56.67-NR) and median overall survival of 33 patients in the no HIPEC group with PSDSS I - IV was 23.17 months (95%CI 6.33 - 61.17) ($p < 0.0001$) (**Table 2**). Three and five years overall survivals were 71.39% and 55.44% in the CRS and HIPEC group and 32.45% and 32.45% in the no HIPEC group, respectively.

There were 30 patients with E-PSDSS 0 (7 with HIPEC and 23 without HIPEC). At a mean follow-up of 21.10 months and 48.53 months, the 23 patients without HIPEC and 7 patients with HIPEC were alive. We excluded all these 30

Table 2. Median overall survival in no-HIPEC and HIPEC groups.

	N	Median survival* (95 CI%)	p
E-PSDSS (I - IV)	199		**<0.001**
- HIPEC	166	76.6 (56.67-NR)	
- NO HIPEC	33	23.1 (6.33 - 61.17)	
E-PSDSS I	56		
- HIPEC	48	NR	
- NO HIPEC	8	NR	
E-PSDSS II	48		**0.0001**
- HIPEC	46	NR	
- NO HIPEC	2	NR	
E-PSDSS III	20		**0.8084**
- HIPEC	19	76.6 (32.8 - 76.6)	
- NO HIPEC	1	NR	
E-PSDSS IV	75		**0.0004**
- HIPEC	53	29.9 (21.9 - 37.3)	
- NO HIPEC	22	8.9 (4.07 - 23.17)	

*Months.

patients from the final comparative survival analysis in Table 2 because they include patients with non-perforated tumors and no evidence of peritoneal dissemination. At the time of analysis, they all are alive and without evidence of disease.

All 56 patients (48 in HIPEC group and 8 in the no HIPEC group) with E-PSDSS I are alive.

Median survival for the 48 patients (46 in the HIPEC group and 2 in the no HIPEC group) with E-PSDSS II has not been reached (NR). However, their survival difference is significant with $p = 0.0001$.

Median survival of 19 patients with HIPEC and 1 patient in the no HIPEC group with E-PSDSS III were 76.6 months (95% CI 32.8 - 76.6) and not reached, respectively ($p = 0.8084$).

Median survival of 53 patients with CRS and HIPEC and 22 patients in the no HIPEC group with E-PSDSS IV were 29.9 months (95% CI 21.9 - 37.3) and 8.9 months (95% CI 4.07 - 23.17), respectively ($p = 0.0004$) (Table 2).

When stratifying the 173 patients undergoing CRS and HIPEC by the severity of their peritoneal disease, 5-year overall survival was 100%, 100%, 84.46%, 52.29% and 12.92% for E-PSDSS 0, I, II, III and IV, respectively ($p < 0.0001$) (Figure 2). Please note that the lines for E-PSDSS 0 and 1 are superimposed as all these patients are alive.

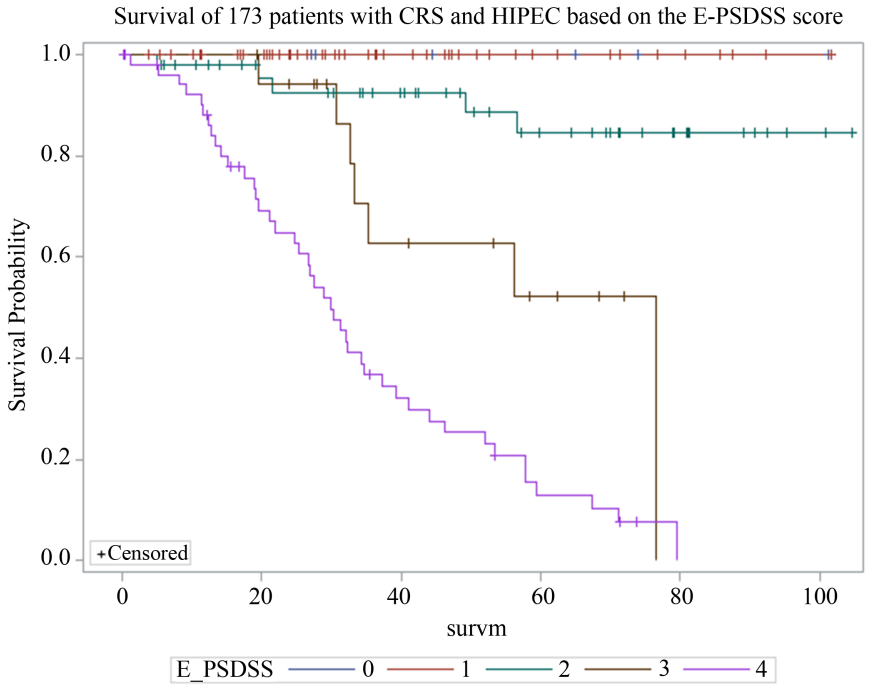

Figure 2. Survival of 173 patients with CRS and HIPEC based on the E-PSDSS score.

A univariate and multivariate analysis was performed on the survival of patients undergoing CRS and HIPEC. With the univariate analysis, significant difference in survival was associated with female sex versus male sex ($p < 0.0001$); E-PSDSS Stage 0, I, II, III, or IV ($p < 0.0001$); E-PSDSS stage 0/I versus II ($p = 0.0307$); E-PSDSS Stage III versus IV ($p = 0.003$); E-PSDSS groups 0, I & II versus III/IV ($p < 0.0001$).

When these factors were re-examined in the multivariate analysis, sex (HR female vs male 0.562 [95% CI 0.318, 0.99]; $p = 0.0462$) and E-PSDSS stage [0, I, II, III, IV] (HR 0 vs IV NR, HR 1 vs IV NR, HR II vs IV 0.072 [95% CI 0.028, 0.189], HR III vs IV 0.353 [95% CI 0.158, 0.791]; $p < 0.0001$) were identified as independent predictors of survival (**Table 3**).

A Cox PH regression model was performed which included the factors of CRS and HIPEC surgery (yes and no), E-PSDSS (Stages 0, I, II, III and IV) and the interaction of CRS and HIPEC surgery with E-PSDSS stage. The last term assess if the survival differences between CRS and HIPEC surgery (yes vs no) are about the same across the E-PSDSS stages. The analysis found that the interaction term was not statistical significant ($p = 0.1539$) which suggests within the sensitivity of the analysis, the survival difference between CRS and HIPEC surgery (yes vs no) are about the same for different E-PSDSS stages. It should be emphasized that the sensitivity of this analysis is limited due to the limited number of patients who did not receive CRS and HIPEC surgery.

When the interaction term was removed from the model, both individual terms were statistically significant (CRS and HIPEC surgery ($p = 0.0003$) and E-PSDSS stage ($p < 0.0001$)).

Table 3. Univariate and multivariate analysis of factors associated with survival in HIPEC-group.

Characteristic	N	UNIVARIATE		MULTIVARIATE	
		Median survival** (95% CI)	p (1)	HR (95% CI)	p (2)
AGE (years)			0.3683		0.0806
- <50	70	67.4 (44.13-NR)			
- 50 - 70	92	NR (59.33-NR)			
- >70	11	56.6 (27.43-NR)			
SEX			**<0.0001**	0.562 (0.318 - 0.990)	**0.0462**
- F	100	NR (76.6-NR)			
- M	73	49.23 (32.8 - 79.5)			
E-PSDSS			**<0.0001**		**<0.0001**
- STAGE 0	7	NR (NR-NR)		NR (NR-NR)	
- STAGE I	48	NR (NR-NR)		NR (NR-NR)	
- STAGE II	46	NR (NR-NR)		0.072 (0.03 - 0.18)	
- STAGE III	19	76.6 (32.8 - 76.6)		0.35 (0.16 - 0.79)	
- STAGE IV	53	29.93 (21.9 - 37.3)			
E-PSDSS			**<0.0001**		**<0.001**
- STAGES 0 - II	101	NR (NR-NR)			
- STAGES III - IV	72	33.3 (28.9 - 44.13)			

** Months: 1 Based on log Rank Test; 2 Based on Cox proportional Hazard Model.

4. Discussion

It has been 42 years since Dr. John Sprat from the University of Louisville, Kentucky did the first combination of cytoreductive surgery (CRS) and HIPEC in a young patient with Pseudomyxoma Peritonei of appendiceal origin [8]. Since then, our understanding of the biological behavior of different mucinous tumors of the appendix has changed significantly [9]. We recognized that not all patients with mucinous peritoneal implants from an appendiceal tumor are Pseudomyxoma Peritonei (PMP) [10]. We also recognized that the outcome from CRS and HIPEC is not the same on all of these patients. However, after all this time, we still do not know how to counsel every patient that has been diagnosed with a mucinous appendiceal tumor. Analysis of this current data suggests that not all will need CRS and HIPEC (those with E-PSDSS 0) and that in some of those patients that do, this multimodality treatment can be done via the open or the laparoscopic route [11]. We believe that the ideal treatment of a cancer patient

should be to provide the most up to date available therapies in the right sequence. The challenge is to identify prognostic indicators that can help us make those recommendations in order for the patients to make an informed decision about their care. Our obligation is to maximize benefits, minimize morbidity and avoid therapies that only offer false hope. When it comes to management of patients with appendiceal tumors, there are no NCCN (National Comprehensive Cancer Network) guidelines [12]. Level 1 evidence from prospective randomized trials that would offer Grade A recommendations is just not feasible due to low incidence of these tumors, the discrepancy on terminologies and the lack of cooperation between us, healthcare providers.

Significant progress has been made with the 8th edition AJCC/TNM staging and the College of American Pathologists (CAP) nomenclature. As stated before, the grade of the tumor has been added. However, when we analyze the patients included in this series (**Figure 1**) we see that most of the patients are Stage IV and that there is a tremendous difference in survival between Stage IVA and Stage IVB. In addition, the current study demonstrates that it is also very important to include the extent of disease in the staging of these patients. **Figure 3** demonstrates the prognostic significance of tumor burden. Meanwhile, it appears that the discriminating value of the T stage system is very limited as almost all tumors will be T4 in order to develop peritoneal dissemination. We also know that the N stage does not have a significant impact in patients with established carcinomatosis. When it comes to the M status is not just the presence or absence of metastasis. Our analysis suggests that the G (Grade) and E (Extent) status, are the two most important prognostic indicators at the present time. The outcome of a patient with a large tumor burden from a true pseudomyxoma

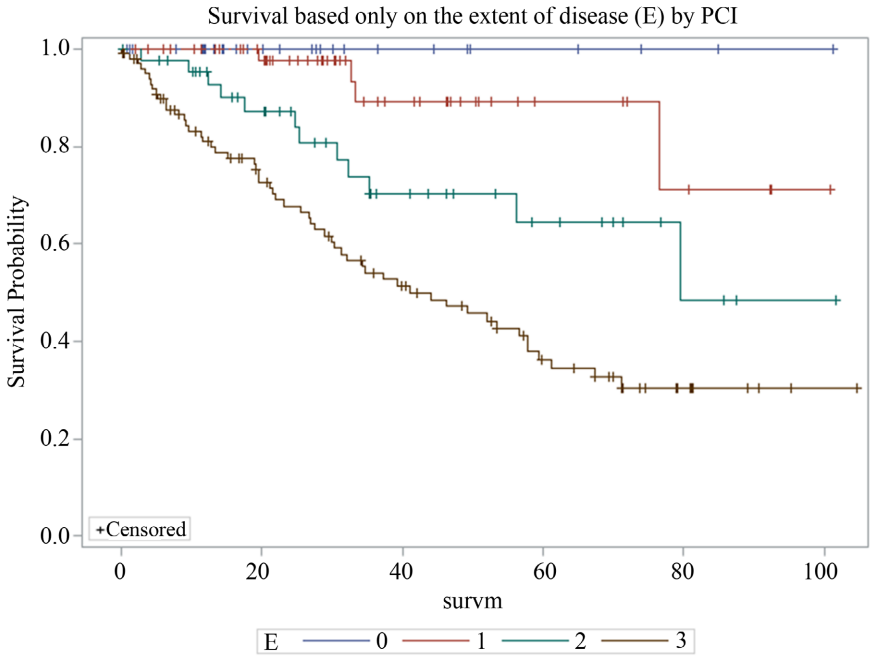

Figure 3. Survival based only on the extent of disease (E) by PCI.

peritonei is better than the one of a patient with moderate tumor burden from a signet ring cell carcinoma.

Therefore, we believe that the E-PSDSS (T, N, M, G, E) fulfills most of the objective information to determine not only prognostic significance but also the number and sequence of currently available treatments that are necessary. This information is readily available and reproducible utilizing these 5 clinico-pathological variables (TNMGE). Table 1, Limitations of this second edition of the PSDSS include the difficulty of introducing something new; it takes time for it to become adopted by the healthcare providers treating these patients. Also, it does not include any molecular parameters that are becoming more relevant in many cancer types.

Our ongoing challenge is to individualize the care of all patients, those with and those without peritoneal dissemination from mucinous appendiceal tumors. Much work still needs to be done but having a reporting system as described by the CAP is the most important first step as the reporting should be done as it is done in other solid tumors: Objective analysis by a pathologist, not by grouping patients based on the prognosis of their metastatic tumors. These are standards that are understood and followed by all pathologists around the world; eliminating much of the difficulties associated with confusing terminologies.

Future directions will include the incorporation of gene expression profiles and determination of proliferation indices [13] to the current severity score, E-PSDSS, allowing us to stratify homogenous groups of patients into multi-institution studies that will produce practice altering data, maximizing benefits and minimizing morbidity in this challenging group of patients with an uncommon diagnosis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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